

Attorney Docket No.: 930008-2202 (BOE0003US.NP)
Inventors: Klokke et al.
Serial No.: 10/541,894
Filing Date: December 2, 2005
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Amendments to the Specification:

Please replace the first and second paragraphs at page 9 with the following rewritten paragraphs:

--Suitable lipophilic retarding agents (= fat matrix-forming agents) are, for example

- fatty alcohols, such as stearyl alcohol;
- mono-, di- and tri-glycerides, such as glycerol monostearate, ~~precirel~~ PRECIROL (glycerol palmitostearate) or ~~Compritel~~ COMPRITOL (glycerol monobehenate with 0.2-0.3 % magnesium stearate);
- hydrogenated vegetable oils, such as hydrogenated castor oil (~~Cutina~~ CUTINA HR);
- waxes, such as beeswax, carnauba wax or microcrystalline wax.

As preferred lipophilic retarding agents, glycerol monobehenate and/or hydrogenated castor oil are/is used. The fat matrix-forming agents are present in concentrations of from 5 to 60 % by weight, especially from 10 to 50 % by weight, based on the total weight of the pharmaceutical form.

In combination with one or more fat matrix-forming agents there may also be used hydrogel matrix-forming agents, such as, for example, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, ethyl hydroxyethyl cellulose, hydroxyethyl cellulose, methyl cellulose, alginates, ~~carbomer~~ CARBOMER (polyacrylic acids), sodium carboxymethylcellulose, tragacanth, rubber or gelatine. Those polymers are able to hydrate and form a gel-like layer that

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is capable of releasing the active ingredient slowly by diffusion and erosion.--

Please replace the paragraph bridging pages 9 and 10 with the following rewritten paragraph:

--Suitable oily substances are neutral oil, sesame oil, peanut oil, olive oil, almond oil, castor oil, soybean oil, coconut oil, cottonseed oil, corn oil, rape oil, sunflower oil, wheat kernel oil and liquid paraffin. Wax solutions in organic oil, or low-viscosity wax, can also be used. Neutral oil is especially preferred. Neutral oil (~~Miglyol~~ MIGLYOL) is understood to mean a mixture of short- and medium-chained triglycerides, mainly with the fatty acids caprylic acid (C8) and capric acid (C10). The ~~Miglyols~~ MIGLYOLS also include esters with propylene glycol. ~~Miglyol~~ MIGLYOL 812 is preferred. The oily substances are present in concentrations of from 0.2 to 20 % by weight, especially from 1 to 7.5 % by weight, based on the total weight of the granules.--

Please replace the first full paragraph at page 10 with the following rewritten paragraph:

--The following excipients can be used in the granule preparation: flow-regulating agents, such as, for example, ~~Aerosil~~ AEROSIL, talc; granule binders, such as, for example, gelatine, starch paste, methyl cellulose, carboxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, pectin-slime, polyvinylpyrrolidone, polyvinyl acetate and/or polyvinyl alcohol; dry binders, such as, for example,

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microcrystalline cellulose, starch, modified starch, lactose and/or saccharose; solvents for a granulating solution, such as, for example, water, ethanol, isopropanol, acetone or mixtures thereof; disintegrants, such as, for example, sodium carboxymethyl starch, crospovidone; wetting agents, such as, for example, sodium lauryl sulphate or sodium docusate.—

Please replace the table at page 11 with the following rewritten table:

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Constituents	Percentage (%)	Weight (mg/tablet)
Tilidine hydrochloride semihydrate	25.7	102.87
Naloxone hydrochloride	2.3	8.80
Hydroxypropyl methyl cellulose	10.5	40.00
Aerosil <u>AEROSIL</u>	0.5	2.00
Hydrogenated castor oil	17.9	68.50
Compritol <u>COMPRITOL</u>	17.0	64.89
Kollidon <u>KOLLIDON</u>	1.96	7.50
Neutral oil	5.0	19.11
Purified water		150.0
Tablettose <u>TABLETTOSE</u>	16.6	66.38

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Magnesium stearate	0.52	2.0
Total	100	382.1

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Please replace the first full paragraph at page 11 with the following rewritten paragraph:

--Tilidine hydrochloride semihydrate, naloxone hydrochloride, hydroxypropyl methyl cellulose, Aerosil AEROSIL, hydrogenated castor oil and ~~Compritol~~ COMPRITOL are weighed out, sieved and then mixed in a fluidised bed granulator. The resulting mixture is sprayed in the fluidised bed granulator with neutral oil and then with a granulating solution of ~~Kollidon~~ KOLLIDON in water. The granules so obtained are dried in the fluidised bed granulator. After sieving through a 1 mm sieve, readily free-flowing granules are obtained. The granules are mixed in a free-fall mixer with ~~Tabletose~~ TABLETTOSE and magnesium stearate and compressed to form tablets each weighing 382 mg.--

Please replace the table at page 12 with the following rewritten table:

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Constituents	Percentage (%)	Weight (mg/tablet)
Tilidine mesylate	29.8	119.25
Naloxone hydrochloride	2.2	8.80

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Microcellae <u>MICROCELLAC</u>	17	67.95
Hydroxypropyl methyl cellulose	10	40.00
Aerosil <u>AEROSIL</u>	0.5	2.00
Hydrogenated castor oil	17.1	68.50
Compritol <u>COMPRITOL</u>	20	80.00
Kollidon <u>KOLLIDON</u>	1.9	7.50
Castor oil	1	4.00
Purified water		150.0
Magnesium stearate	0.5	2.00
Total	100	400.0

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Please replace the table in Example 3 at page 13 with the following rewritten table:

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Constituents	Percentage (%)	Weight (mg/tablet)
Tilidine mesylate	31.2	119.25
Naloxone hydrochloride	2.3	8.8
Hydroxypropyl methyl cellulose	10.5	40.00
Aerosil <u>AEROSIL</u>	0.5	2.00
Hydrogenated castor oil	17.9	68.50

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Compritol <u>COMPRITOL</u>	17.0	64.89
Kollidon <u>KOLLIDON</u>	1.96	7.50
Neutral oil	5.0	19.11
Purified water		150.0
Tabletose <u>TABLETTOSE</u>	13.1	50.0
Magnesium stearate	0.52	2.0
Total	100	382.1

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